Sub C5

45. A method of delaying or repressing the expression of a target gene in an animal cell, comprising transfecting said animal cell with a synthetic gene, wherein said synthetic gene comprises multiple structural genes, wherein each of said structural gene sequences is separately placed under the control of a promoter which is operable in said cell, and wherein each of said structural genes comprises a nucleotide sequence which is substantially identical to said target gene or a derivative of said target gene, wherein at least one of said structural gene sequences is placed operably in the sense orientation under the control of an individual promoter sequence.

REMARKS

In the Office Action dated May 10, 2000, claims 1-5 are under consideration. In response to the rejections and objections set forth in the Office Action, Applicants have amended the claims which, when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

By way of the foregoing amendment, claim 5 has been canceled without prejudice. Claims 1-4 have been amended. Claims 34-45 have been added. Applicants respectfully submit that such amendment is fully supported by the present specification. No new matter is introduced.

More specifically, claims 1-4 have been amended to more particularly delineate the synthetic gene as capable of "delaying, repressing or otherwise reducing the expression of a target gene in an *animal* cell". Support for the recitation "delaying, repressing or otherwise reducing the expression of a target gene" is found in the specification, for example, at page 1, lines 8-9 and 28-29. Support for the term "animal cell" is found in the specification, for example, at page 22, lines 20-21, page 23, lines 1-3 and Figures 1-28.

Claim 1 has been amended to clarify that the structural gene sequence of the synthetic gene is placed operably *in the sense orientation* under the control of a promoter sequence which is operable in the cell. Support for the recitation "in the sense orientation" is found in the specification, e.g., at page 6, lines 28-29; page 11, lines 28-29; page 14, lines 11-17; page 15, lines 1-3 and Figures 1, 5, 9, 10, 12-20, 22-23, 25-28.

Claim 2 has been amended to clarify that at least one of the multiple structural gene sequences under the control of a single promoter sequence is placed operably in the sense orientation under the control of that promoter sequence. Support for this amendment can be found, for example, in Figures 1, 5, 9, 10, 12-20, 22-23 and 25-26.

Claim 3 has been amended to clarify that at least one of the multiple structural gene sequences is placed operably in the sense orientation under the control of an individual promoter sequence. Support for this amendment can be found, for example, in Figures 19-21.

Claim 4 has been amended to depend on claims 1-3.

Added claim 34 is consistent with amended claim 2, and includes the additional recitation that at least one other of said multiple structural gene sequences is placed operably *in the antisense orientation* relative to the same promoter sequence that drives expression of the (at least one) structural gene sequence placed operably in the sense orientation. Support for claim 34 can be found in the specification, for example, at page 18, lines 11-25 and Figures 14 and 15.

Added claim 35 is consistent with amended claim 3, and includes the additional recitation that at least one other of said multiple structural gene sequences is placed operably in the antisense orientation under the control of a promoter sequence that is different from the promoter sequence that drives expression of the (at least one) structural gene sequence placed

operably in the sense orientation. Support for claim 35 can be found in the specification, for example, at page 18, lines 11-25 and Figures 20 and 21.

Added claim 36 is consistent with new claim 34, and includes the additional recitation that the (at least one) structural gene sequence and the (at least one) other structural gene sequence are spaced from each other by a nucleic acid stuffer fragment, as disclosed in the specification, for example, at page 19, lines 14-30, page 20, lines 1-22 and Figure 15.

Added claim 37 depends from new claim 36, and includes the additional recitation that the (at least one) structural gene sequence, the stuffer fragment and the (at least one) other structural gene sequence comprise an interrupted palindrome, as disclosed in the specification, for example, at page 18, lines 11-25, page 20, lines 16-22 and Figure 15.

Added claim 38 is drawn to a cell comprising the synthetic gene of any one of claims 1-3 or 35-37. Support for claim 38 can be found, for example, in original claim 5 (now cancelled).

Added claim 39 is drawn to a cell comprising a genetic construct which comprises the synthetic gene of any one of claims 1-3 or 35-37 and at least one of an origin of replication or a selectable marker gene. Support for claim 39 can be found in the specification, for example, at page 24, lines 26-29.

Added claims 40-45 are drawn to methods of delaying or repressing the expression of a target gene in an animal cell by transfecting the animal cell with a synthetic gene. Support for claims 40-45 are found throughout the specification and e.g., at pages 23, lines 9-15.

Claim 5 is objected to as allegedly written in improper form. The Examiner indicates that it is improper for claim 5, written as a multiple dependent claim, to depend from

a claim which is itself a multiple dependent claim. Claim 5 is further rejected under 35 U.S.C. §101 as allegedly drawn to non-statutory subject matter, as the Examiner contends that the term "organism" encompasses human. Claim 5 is also rejected under 35 U.S.C. §112, second paragraph, as the Examiner contends that the term "as described herein" is indefinite.

Applicants respectfully submit that the above objection to and rejections of claim 5 are rendered moot in view of the cancellation of claim 5, and withdrawal thereof is therefore respectfully requested.

Claims 1-5 are rejected under 35 U.S.C. §112, first paragraph as allegedly not enabled by the specification.

The Examiner first alleges that the specification does not adequately teach what other sequences may be added in the construct in addition to those sequences specifically disclosed.

Applicants respectfully disagree with the Examiner. Applicants submit that the Examiner has not identified what those additional sequences can or should be. It is submitted that the instant specification adequately teaches one skilled in the art how to make and use the claimed invention. In particular, the specification teaches the essential characteristics of the claimed synthetic genes and genetic constructs, e.g., the structural gene(s) required for downregulation of the endogenous or target gene (see for example page 7, line5 through page 11, line 26), promoters (see for example page 12, line 6 through page 14, line 9 and the Figures), transcription terminators (see for example page 22, line 16 through page 23, line 3 and the Figures), origins of replication (see for example page 23, lines 21-29 and the Figures) and selectable marker genes (see for example page 24, lines 1-15 and the Figures).

The Examiner further contends that the claims read on a number of allegedly non-enabled embodiments such as a "gene" and "alleles". It is the Examiner's opinion that, because the art does not provide an accepted definition for the term "gene", and because different genes have divergent functions, the specification is not enabling as to how to use the claimed invention. Specifically, the Examiner alleges that the genes to be modified in a cell, tissue, organ or organism in accordance with the present invention can not be determined.

In this regard, Applicants respectfully direct the Examiner's attention to the respective definitions in the specification for the terms "gene" (page 6, lines 17-29), "synthetic gene" (page 7, lines 1-3), "structural gene" (page 7, lines 5-14) and "target gene" (page 7, lines 17-20). Applicants further submit that a principal feature of the present invention is directed to synthetic genes which downregulate the expression of a target gene in an animal cell, wherein the synthetic genes comprise structural gene sequences, each of which comprise a nucleotide sequence substantially identical to the nucleotide sequence of the target gene (or a derivative thereof), and wherein at least one of the structural genes is placed in the sense orientation relative to the promoter. Thus, it is submitted that the subject invention may be applied to downregulate expression of any target gene in an animal cell.

The Examiner also contends that the instant claims relate to the art of gene therapy, which was regarded at the time of the instant filing as highly unpredictable. The Examiner argues that the specification does not describe a single working example that demonstrates the delivery or expression of any synthetic gene in an animal.

Applicants respectfully disagree with the Examiner. Applicants submit that the success of gene therapy has been documented in treating a variety of clinical disorders, and that gene therapy has been the subject of a number of U.S. patents. See, e.g., U.S. Patent No.

5,705,151, U.S. Patent No. 5,658,565 and U.S. Patent No. 5,656,465. In light of the teachings of the present invention, those skilled in the art are fully enabled to make and use the claimed invention.

However, in an effort to favorably advance the prosecution of the present case, Applicants have amended the claims to recite downregulation of the expression of a target gene in an *animal cell*. It is submitted that there were established methodologies at the filing date of the application at least to transfect animal cells with nucleic acid molecules to produce transiently or stably transfected animal cells. Therefore, it is submitted that, in light of the teachings provided in the present specification and the established prior art methodologies, those skilled in the art are fully enabled to make and use the claimed invention without undue experimentation.

Accordingly, Applicants respectfully submit that the rejection of claims 1-5 under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is therefore requested.

The Examiner has also rejected claims 1-5 under 35 U.S.C. §102(b) as allegedly anticipated by Wang et al. (*Proc. Natl. Acad. Sci. USA* 94: 11563, 1997). The Examiner contends that Wang et al. teach a Factor IX targeting vector with multiple structural gene sequences (page 1153 and Figure 1). The Examiner contends that Wang et al. also teach homologous recombination (page 11565, Figure 2). Thus, the Examiner concludes that the Wang et al. reference anticipates claims 1-5.

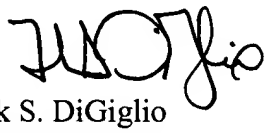
Applicants respectfully submit that Wang et al. do not teach or suggest the claimed invention. The present claims are drawn to synthetic genes, genetic constructs, cells transfected with such genes or constructs, and methods of downregulating a target gene in an

animal cell. The synthetic genes in the present claims, which are characterized as capable of delaying, repressing or otherwise reducing the expression of a target gene in an animal cell, comprise at least one structural gene sequence placed operably in the sense orientation under the control of a promoter sequence which is operable in an animal cell. In contrast, Wang et al. do not teach or suggest a synthetic gene which comprises at least one structural gene sequence placed operably in the sense orientation under the control of a promoter sequence which is operable in an animal cell. Neither do Wang et al. teach or suggest a synthetic gene capable of delaying, repressing or otherwise reducing the expression of a target gene in an animal cell. Applicants submit that a rejection of a claim under 35 U.S.C. §102(b) requires that the single prior art reference disclose *every* element of the claim. The absence from the reference of any claimed element negates anticipation. Kloster Speedsteel AB v Crucible Inc., 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).

Accordingly, Applicants submit that the Examiner's rejection of claims 1-5 under 35 U.S.C. § 102(b) is overcome. Withdrawal of the rejection is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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